

foods on metabolism probably is related to vitality and stamina, and should be numbered among the favorable effects of protein as a nutrient. At the same time the pronounced heating effect of protein associated with its stimulating action on metabolism, will naturally and rightly lead to a seasonal variation in the popularity of protein-rich foods.

This abbreviated consideration of the importance of protein in the dietary, involving a study of the waste incidental to its utilization by the body, its proper function in the body, and its physiological effects, illustrates how complicated the problem of protein requirements has be-

come and how difficult it is to make hard and fast recommendations. In pedagogy the subject of protein requirements is still the despair of the teacher of the physiology of nutrition.

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THE CONTROL OF DIPHTHERIA

WILLIAM H. PARK, M.D., M. C. SCHRODER, M.D., ABRAHAM ZINGHER, M.D.

From the Bureau of Laboratories, New York City Health Department

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SINCE 1892 three different measures have been introduced which have had a marked effect upon the methods used by health authorities in the attempt to control the spread of and the mortality from diphtheria.

The first was the employment of throat cultures to detect carriers of diphtheria bacilli and to help in the diagnosis of doubtful cases of this disease. It became the almost universal practice to make cultures from doubtful cases and when these were positive to isolate the patients. The quarantine was continued until two cultures free from diphtheria bacilli had been obtained. To a lesser extent children and other persons in contact with cases of diphtheria were cultured in order to detect carriers. This was sometimes done in families but was more frequently practiced in schools and

institutions. The results accomplished by cultures were much less however, than we had hoped for. There were a number of reasons for this partial failure. First, there was the uncertainty of relying on culture results in carrier cases. It was soon discovered that a culture from the throat of a convalescent patient or from a healthy throat might be negative and yet bacilli be present in some portion of the throat other than from which the culture was made. For this reason two cultures were demanded instead of one. Necessarily if a single negative culture is not conclusive, a second culture is also not absolutely conclusive. If the two agree it simply makes the negative results from the first culture more dependable.

Some years ago we made as many as six successive cultures from the throats

of a large number of inmates of an insane hospital and found sometimes, three, four or five cultures negative and then the next culture positive. In such cases it is possible but not probable that infection occurred in a period between the last negative and the first positive culture. Second, it was recognized that diphtheria carriers were scattered everywhere. It was found for instance that from one to two per cent of the child population in New York City are diphtheria carriers on any given day during the winter time and that at least fifty per cent of all cases of diphtheria develop in children who have had apparently no contact with cases of diphtheria. In these cases the thousands of carriers must be presumed to be the transmitters of infection. Third, the necessity for immediate information forces the laboratory to report the result of a smear from a throat culture as positive without the confirmation of a virulence test. This is making a more definite statement than our knowledge really permits. All we know is that diphtheria-like bacilli are present in the culture. These may not be virulent. Knowing this fact we hesitate to adopt drastic procedures and we should always be ready to make a virulence test in any case in which the persistence of the diphtheria-like bacilli makes a real hardship for the patient. The more doubtful the clinical diagnosis in a case, the more likely will the bacilli present be diphtheria-like rather than true diphtheria bacilli.

In spite of these drawbacks the examination of cultures has remained one of the very important measures that we use in controlling diphtheria. They explain, however, why the use of cultures cannot be applied to the general population but is limited to those who are suspected to have been in contact with diphtheria, to have diphtheria or to have recently recovered from it. For that and other reasons cultures have had only a moderate effect on the total amount of diphtheria in a community.

The next important means of controlling diphtheria was diphtheria antitoxin. As a measure for producing immunity for a short time, this proved to be absolutely reliable. Owing to the fact that diphtheria antitoxin is not a product of human cells but is made by the cells of the horse, it disappears gradually after injection from the human body, so that at sometime between two and four weeks, the antitoxin is dissipated and the immunity disappears. If desirable the injections can be repeated at intervals. The antitoxin, however, is eliminated twice as rapidly from these later injections and must therefore be given every ten days. Antitoxin has been most successfully used as a preventive in those who are in direct contact with cases of diphtheria, such as children in a family in which diphtheria has developed or in institutions in which an outbreak of diphtheria has occurred. The only precaution necessary is not to give antitoxin as a preventive to children showing physical characteristics of status lymphaticus or giving a history of having had attacks of asthma.

The two most striking instances in our own experience in the control of diphtheria occurred one in 1894 and the other in 1915. In the first an outbreak in a large children's institution was controlled by giving every inmate a dose of 300 units of antitoxin. The other was a large insane asylum where some forty cases had developed within twenty-four hours. The 3,500 inmates were each injected with 1,000 units of antitoxin. No more cases developed in either institution. For a number of years our inspectors in New York City yearly injected between ten and fifteen thousand children belonging to families in which diphtheria occurred. For each thousand children injected there averaged two cases of mild or suspected diphtheria. None of these were severe and with our present knowledge we know that many, at least, were suffering from tonsilitis due to the pyogenic cocci but because of their contact with cases of

diphtheria these patients were temporarily diphtheria bacillus carriers.

The use of cultures in those who were suspected to harbor the germs, and the use of antitoxin in those who were in definite danger of infection diminished considerably the number of cases of diphtheria but still left at the close of twenty-five years of effort the development of about two-thirds as many cases as formerly occurred. The use of antitoxin in treatment was of course far more efficient because it could be used in every case as soon as it was discovered, but antitoxin for prevention could only be used where danger was apparent from contact. Through the use of antitoxin the deaths have been cut down to about one-seventh of what we estimate they would otherwise be. The fact that the improvement which continued for many years after the introduction of antitoxin has ceased and that in fact a few years ago diphtheria began to increase slowly in the United States, made us appreciate that we had reached about the limit of what we could do with the old measures. It made us think seriously of using active immunization. This was with the hope of rendering the population permanently immune rather than of waiting for cases to develop and then trying to cure them and to prevent the further spread of the contagion.

REASONS WHICH DELAYED THE USE OF TOXIN-ANTITOXIN AS AN IMMUNIZING AGENT IN MAN

The fact that animal experimentation in the hands of Babes, ourselves and others had shown that after the injections the antitoxin would take a number of weeks to develop in those not originally possessing it, made the toxin-antitoxin of no immediate value to persons in imminent danger of infection. Therefore, in the presence of diphtheria, immunizing antitoxin injections would still be necessary in families and institutions. Furthermore, Theobald Smith's observations indicated that the immunity from toxin-

antitoxin injections in animals lasted for not more than about two years. If human beings lost their acquired immunity as soon as this, it would necessitate repeating the injections in children every two years which would be to attempt to accomplish an almost impossible task. The success of the treatment would also be difficult to determine. Either very large numbers of treated children would have to be watched and compared with untreated children as to the development of diphtheria or from time to time bleedings from them would be necessary to test for the presence of antitoxin. In the absence of any simple test for determining which individuals had natural antitoxin and which did not, we were under the necessity of injecting many unnecessarily if active immunization were to be attempted.

The publication by Schick in the fall of 1911 of his intracutaneous test and in 1913 of its application as a practical test for immunity in the presence of exposure gave a simple means of testing for antitoxic immunity before and at intervals after the injections.

FIRST PRACTICAL APPLICATION OF DIPHTHERIA TOXIN-ANTITOXIN IN MAN

Von Behring on May 8th, 1913, reported the early results of the injections of neutralized toxin in a small number of persons. Most of them received one or two doses. Before giving the injections he used no Schick tests or other means of testing whether or not the cases were already immune. He did not use the Schick test after the injections. The onset of the War cut short his investigations. With our present knowledge we appreciate that he demonstrated that the toxin-antitoxin mixture could be safely given in children and that those who already possessed antitoxin showed within a short time an increased amount. He did not originate the mixture nor establish the fact that those who had no antitoxin, developed it.

THE ANTITOXIN RESPONSE AND THE PERMANENCE OF THE IMMUNITY ACQUIRED

Late in 1913, we began the practical use of toxin-antitoxin injections controlled by the Schick test for the immunizing of children against diphtheria and established the facts that the procedure was harmless and that after three injections about eighty per cent of those individuals possessing no antitoxin or insufficient antitoxin to protect from diphtheria, developed immunity. Those showing positive Schick reactions and receiving two injections, developed negative Schick reactions in about fifty per cent. We then realized that the next important problem was the duration of the antitoxic immunity in those who had developed antitoxin. A satisfactory answer to this question required that immunizations be carried out in institutions where the children would be under observation for a number of years. A few suitable institutions were immediately sought for and obtained and, later, a few schools were added. We have thus been able to keep under supervision for from three to six years some ten thousand children. From year to year we are re-applying the Schick test to these original children, both those who gave negative Schick tests before the injections and those who were negative after the injections. With a few of them we are now beginning the seventh year of observation. With very few exceptions all the children who developed antitoxic immunity, have retained it during these six and one-half years. We have had no serious immediate or late after-effects. In these institutions diphtheria has not developed in any child who has received three injections. Eighty per cent of those who received three inoculations have developed sufficient antitoxin within three months to prevent the positive Schick reaction. Fifty per cent of the remainder developed antitoxin immunity sufficient to give the negative Schick test

before the end of the first year. The remainder received then or later, a second series of injections and all of these concerning whom we have information became immune. In some later investigations, we have met with an occasional child who resisted even two series of injections.

IMMUNIZATION OF SCHOOL CHILDREN AND CHILDREN OF PRE-SCHOOL AGE

Impressed by these results we determined to introduce the practice of immunization with toxin-antitoxin as widely as possible. Statistics on diphtheria verify the clinical experience of the high morbidity and mortality from the disease in young children. From 80 to 85 per cent of deaths from diphtheria occur in children under the age of five years. This group, therefore, represents the most important part of the population that has to be protected against diphtheria and the most suitable for immunization.

In proportion to the importance of the immunization of this group, however, are also the difficulties that have to be met and overcome. These young children are scattered in the individual homes and cannot be reached like school children in large groups. The parents have to be seen and convinced before they will give consent for the immunization of their children. All this requires considerable effort and time on the part of the health officer and the public health nurse. After arrangements have been perfected the parents must bring their young children to the physicians or the latter must go to the homes of the children. This entails a considerable loss of time to the mother or physician and thus adds to the difficulty and expense of giving the preventive treatment. For these and other reasons we determined to begin with the school children as there were very decided advantages in so doing. For instance, it was deemed wise to acquaint as many parents and others as

possible, with the value of the Schick test and the toxin-antitoxin injections. No better way seemed available than to use the schools as the means of doing this. If each pupil presented his parents with a circular picturing the danger from diphtheria, describing the preventive treatment and asking for permission to administer this treatment if the family physician approved, it would mean that nearly a million adults and a million children would have the arguments for the use of the toxin-antitoxin vaccine presented to them in a favorable way. If, as we hoped, about one-half of the children brought back an acceptance of the offer to give them the toxin-antitoxin, we should be able not only to immunize those shown by the Schick test to possess no antitoxin but, by preventing these children from contracting diphtheria, we should also do much to prevent their carrying diphtheria home to the younger children in their families.

The testing of the school children would also give us the chance to determine exactly what effect the immunization had had. We could make an index of 100,000 children who had been tested and, when Schick positive, had been injected with toxin-antitoxin; a similar index of 100,000 children of the same ages who had refused the test and the injections could be used for comparison. The cases of diphtheria occurring among the children of school age could thus be looked up in either index and observations made as to how many cases of diphtheria occurred in the two groups. We believed that after several years of such observations we would have evidence of convincing value as to the protection guaranteed by a negative Schick test due either to natural antitoxin immunity or to the response to the toxin-antitoxin injections.

Now, at the end of two years we actually have such an index nearly completed. The 90,000 tested children and the 90,000 control children have been gathered about equally from the schools of the

different boroughs; they were collected by the groups of nurses and teachers from the schools which had been tested by Dr. M. C. Schroder and Dr. A. Zingher. The results from four months of observations are very interesting. They are given at the end of this paper.

A very important point is the enlistment of the interests of the principal of a school. As a rule Dr. I. H. Goldberger, of the Bureau of Educational Hygiene of the Department of Education, first prepares the way by obtaining permission for us to do the work in the school. According to the borough in which the school is situated, Dr. Zingher, Dr. Schroder or one of their representatives sees the principal and explains fully the objects we have in view. Literature is left for the teachers. Either the principal or the physician meets the teachers in a conference, gives them the necessary information and tries to arouse their enthusiasm. The success or failure in getting a favorable response from the children or their parents, depends largely on the interest which the principal, the assistant principal and the teachers take in the matter. When they give us their enthusiastic coöperation we expect to obtain consents from three-fourths of the parents; when we fail to arouse the teachers' interest we are fortunate if consents are obtained from one-fourth of the parents.

The preparatory work being finished and the date for the test being determined, we send to the school the circulars and consent slips to be taken by the children to their homes. The consent slips brought back to the school are collected by the teachers; the Schick tests and the toxin-antitoxin injections follow according to the consent slips which each teacher has received.

Two forms of certificates are issued to the children. One form is given to those who are found by the original Schick test to be naturally immune; the other form is given to those who have become immune after toxin-antitoxin in-

jections, as shown by the Schick retest. These certificates are issued only to those who have given the negative Schick reaction. The winning of a certificate thus becomes an incentive to the child to have the retest made. The campaign progressed so rapidly that two-thirds of all the school children had been reached at the time of the closing of the schools last June. Nearly half of these children had received the Schick test. Many additional mothers had been brought in contact with the preventive work through Dr. Schroder's visits to the Baby Health Stations and the injection of about 1,000 babies had been accomplished.

This spring we believed that owing to this preparatory work in most of the homes, where there were children, the parents knew what modern diphtheria prevention meant. In fact many of them asked us where they could take their younger children to have them injected against diphtheria. Taking these facts into consideration we decided to use our trained force for the summer in an intensive drive to reach as many as possible of the younger children.

The work among the children of pre-school age, including those between six months and six years of age, was started on July 1st and carried out during the months of July, August and the first two weeks of September. The injections were given in all the Baby Health Stations of the Department of Health, in similar stations of the New York Diet Kitchen Association, and in many of the Mothers and Babies Play Grounds located during the summer in the play yards of the public schools.

The first step was to notify the parents that they now had the opportunity to have their children, who were too young to go to school, immunized against diphtheria. A carefully worded circular emphasizing the danger of diphtheria for the young children was distributed through the schools just before they closed for the summer vacation. This circular was printed in English, Italian

and Jewish, and gave a list of the Baby Health Stations.

Of these circulars 150,000 were distributed through the public schools. The coöperation of the principals and teachers was solicited in asking the children to take the circulars home to their parents and notify them on what days during the month the doctor would give the injections at a neighboring Bay Health Station. 50,000 additional circulars were distributed through the nurses at the Baby Health Stations, and also through the nurses of the Bureau of Preventable Diseases and of the Henry Street Settlement. The Society for Improving the Condition of the Poor, The Charities Aid Organization and The American Red Cross gave their help. 10,000 circulars were also distributed through private physicians among their own patients. Another circular was distributed by the Metropolitan Life Association agents and by the boy and girl scouts.

A very important and effective method of reaching many parents was through a folded mailing card, which was sent to all those mothers whose babies had been registered at the Baby Health Stations during the years 1920 and 1921, and in some instances also during the years 1918 and 1919.

45,000 of these cards, which were printed in English, Italian and Jewish, were sent out. 5,000 more of the cards and 10,000 of the circulars were posted in the hallways of tenement houses, windows of stores, etc. A Baby Health Contest and gatherings of groups of parents at the schools also afforded opportunities for propaganda work.

In the group working in the Boroughs of Manhattan and The Bronx there were seven part time physicians, four nurses and three laboratory assistants. These were divided into seven teams, each team consisting of a physician and a nurse or a laboratory assistant. Four teams were assigned to the Baby Health Stations and three teams to the Mothers and Babies Play Grounds. The schedule was so ar-

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BABY HEALTH STATION**Important Official Notice****DIPHTHERIA PREVENTION****DEPARTMENT OF HEALTH****CITY OF NEW YORK**

Protect your young children against Diphtheria! Next week the doctor will vaccinate against Diphtheria the children of the Baby Health Station and also all those who are too young to go to school. Be sure to ask the nurse about this wonderful opportunity as soon as you receive this card. She will give you all the information you need. Also tell your neighbors, who have young children, about it. These injections may save your children's lives!

This is a special opportunity which the Department of Health offers to you. Will you not take advantage of it?

The doctor will give the protective injections on.....
during the month of.....

Mailing Card

ranged that each team was assigned to a different station during the six days of the week, returning to the stations on the corresponding days during the entire month. In this way the physician came back to each station during four or five afternoons in one month.

A printed schedule of the Baby Health Stations was distributed to all the nurses of the department and to the various organizations assisting in this campaign. This helped considerably in coördinating the work.

The work in the other three boroughs under Dr. M. C. Schroder was carried out along the same lines except that a part of the force was diverted to a number of large institutions for the double purpose of immunizing the inmates and of testing a new preparation of toxin-antitoxin.

**TOXIN-ANTITOXIN INJECTIONS WITH
THE SCHICK TEST BUT WITH-
OUT THE CONTROL TEST**

Each child was given the Schick test. The control test was omitted, as young

children under five or six years of age very seldom show pseudo reactions that cause confusion.

Although each child received the Schick test, we did not guide ourselves by its results in giving the injections of toxin-antitoxin. The first injection was given at the same time as the Schick test, the second injection a week later and the third injection two weeks later. In giving the toxin-antitoxin injections to all children irrespective of the results of the Schick test, we wished to *emphasize the advisability of immunizing all children between six months and six years of age with three injections of toxin-antitoxin.* It would cause confusion if we gave toxin-antitoxin to children under two years who gave negative reactions and omitted the injections in negative children of greater ages. The parents would not understand that a negative Schick test in a very young child might indicate the persistence of the mother's transferred antitoxin and not a new formation. Some of the mothers never returned with their children. By giving

the first injection with the Schick test we have made certain of at least one injection. Our general opinion is that because of the valuable information obtained it is advisable, when conditions are favorable, but not necessary to give the Schick test to all children after the age of three. At this time they have lost all antitoxin transferred to them by their mothers. The high percentage of positive Schick reactions among children under six years of age and the high death rate from diphtheria in this age group shows how important it is to protect as promptly as possible all young children against diphtheria. It is a fact that many physicians do not give the toxin-antitoxin injections because they hesitate to use the Schick test. Others give the test improperly or read it inaccurately. Under these and similar conditions it is better to give the injections without the test. Another excellent reason for not delaying for a Schick test before giving the toxin-antitoxin injections to all young children is that only a very mild local and

constitutional reaction is produced as a result of the injections.

After the injections of toxin-antitoxin, however, a child should not be pronounced immune to diphtheria until it gives a negative Schick reaction. This test can be made at any time four months or more after the injections. An original Schick test has this great value that, when negative in a child over three years of age, we can assure the parents that the child is probably immune for life.

It is important to remember that the technique of the test and interpretation of the reactions are easily acquired and that every physician should be capable of utilizing accurately this reliable and excellent clinical test. Each child, receiving the full series of three injections of toxin-antitoxin was given the following temporary *Diphtheria Vaccination Certificate*. The final *Diphtheria Protection Certificate* is never issued until a child is found to give a negative Schick reaction.

Diphtheria

Protection

DEPARTMENT OF HEALTH



CITY OF NEW YORK

TEMPORARY CERTIFICATE

This is to Certify that.....age.....

residing at....., has received protective treatment to prevent its having DIPHTHERIA. In a few cases a second treatment is necessary to complete the protection. In six months time bring your child to the Baby Health Station for us to determine by a simple test if your child is fully protected. When it is thus protected this certificate will be exchanged for the permanent or White Certificate.

Issued by.....

ROYAL S. COPELAND, M. D.,

Date

Commissioner

RESULTS OF THE USE OF IMMUNIZING INJECTIONS AMONG THE CHILDREN OF NEW YORK CITY

Sufficient time has not elapsed to make a careful estimate of the effects of the immunizing injections. It must be recognized that the preventive work against diphtheria has consisted not only of giving the injections but also in spreading information of the use of antitoxin.

It is impossible with these two preventive measures, to apportion how much of the improvement belongs to each of them. During the past two years the number of cases in New York City has diminished by twenty per cent and the death rate has decreased from 20 to 16 per 100,000. In the institutions under our care no cases of diphtheria have developed among those who showed a negative Schick test or received three immunizing injections. There have been a very few cases in other institutions which have not been under the supervision of the department in which children showing a negative Schick test have developed mild cases of suspected diphtheria. It has already been stated that the names of 90,000 of the tested children controlled by 90,000 of the names of the untested children have been filed. All cases occurring among the school children during the winter months were looked up in this file. It was found that four times as many children developed diphtheria among the control cases as among the tested cases. The disease was also of much greater average severity in the control cases. Since then, 17 cases whose names were in the file have been admitted to the diphtheria wards of the Willard Parker Hospital. Fourteen of these were among the control cases and three among the tested cases. Not one of these three cases in the Schick negative children showed clinical evidence of undoubted diphtheria and two of the cases contained no diphtheria bacilli. Of the control cases, four were very severely sick with diphtheria. It is our intention

to repeat this winter and the following winters these observations so as to note whether the same difference continues from year to year.

The following table divides all the reported cases of suspected diphtheria as they occurred among the 180,000 indexed children during a period of five months. In the cultures from some of these children diphtheria bacilli were not found.

TABLE I

	Cases Reported by Physicians as Clinical Diphtheria
In Brooklyn:	
26,000 originally Schick-negative children (observation from Oct. 1 to Feb. 15).....	2
15,000 Schick-positive children, 3, 2 or 1 toxin-antitoxin injections	4*
40,000 control children of same ages	27
In Manhattan:	
31,000 Schick-negative children (observation from Oct. 1st to Feb. 15th)	3
19,000 Schick-positive children, 3, 2 or 1 injections.....	5
50,000 control children	29
Summary:	
57,000 Schick-negative children (observation from Oct. 1st to Feb. 15th)	5
33,000 Schick-positive children injected with toxin-antitoxin..	9
Among a total of 90,000 Schick-negative or injected children	14
Among a total of 90,000 control children untreated	56

THE NEW PREPARATION OF TOXIN-ANTITOXIN

Ever since commencing the use of the toxin-antitoxin injections in man, it has been our endeavor to remove as far as possible the annoying protein reactions which follow the immunizing injections. Dr. Banzhaf, who has charge of the chemical side of this study, has up to the present time found it impossible to sep-

*One received only 1 injection. One was shown on retest to be positive. A second series of injections was refused.

arate the autolyzed bacillus substance and other proteins from the specific toxin. This failure to purify the toxin led us to test out the correctness of our opinion that a large amount of nearly neutralized toxin was more valuable than a smaller amount of partially bound toxin. We therefore gathered observations on the results obtained with preparations containing quite different amounts of toxin but always with such additions of antitoxin that one cubic centimeter of each of the mixtures had the same toxic effect in guinea pigs. We noticed that these different preparations gave the same immunizing results but that those having the least amount of toxin and therefore least amount of the accompanying bacillus substance showed the least local reactions. We therefore decided to try

four fatal doses of toxin (one-tenth of an L plus dose of our product, which is about one-thirtieth of the amount in our standard preparation), with the hope of finding that the results would be equally good and the reactions very much less. The results obtained from the different preparations are shown in the two accompanying tables and are very favorable to the new preparation. We believe that the removal of the fear of severe reactions following the injections help greatly to popularize the use of the toxin-antitoxin.

Owing to these favorable reports we have decided to use the new preparation. Owing to the fact that the new preparation is less stable it should be used within three months of its release from the laboratory.

TABLE II

The antitoxin development produced by three injections of mixtures having different amounts of toxin and antitoxin but all causing severe paralysis in guinea pigs receiving doses of 1cc and death within ten days in those receiving 5cc.

Amount of Original Toxin in 1cc. of Mixture	No. of School Children Receiving 3 Injections	Percent of Nonimmunes Shown To Be Immune on Schick Retest 4 Months Later
*1/10 L + (4 lethal doses)	490	90%
1/2 L + (20 lethal doses)	304	95%
3 L + (120 lethal doses)	318	92%
5 L + (200 lethal doses)	487	85%

*The mixture is made by adding three-fourths of a unit of antitoxin to one L + dose of toxin. The toxin and antitoxin should be diluted in cold water and diluted in water at room temperature it deteriorates rapidly. The toxin and antitoxin should be diluted in cold water and diluted in water at room temperature it deteriorates rapidly.

TABLE III

Comparison as to the amount of local and constitutional reaction caused by the new and old preparation.

	*New Preparation 1/10 L +	Old Preparation 3 to 5 L +
No Local Reaction	25%	0%
Slight Local Reaction	64%	41%
Moderate Local Reaction	11%	37%
Marked Local Reaction	0%	22%
Of those showing marked reactions there was a rise of 1°—3° F, and other constitutional symptoms in	0%	6%

*If the 1/10 L + preparation is underneutralized there will be a local reaction from the excess of toxin.